REMARKS

Claims 1, 4-34, 36, 45, 46, 86-90, 157-181, 183, 212, 213, 263-267 and 280-292 are pending in the application. In the Office Action mailed September 30, 2005, claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265 and 280-292 are rejected (claims 46, 88, 212-213 and 266-267 having been withdrawn from consideration as drawn to non-elected species). In the present Amendment, claim 1 has been amended to clarify the claimed invention.

Claim 1 has been amended to clarify that *said method further comprises* measuring the expression level of each of said plurality of different variants of said exon in said at least one gene (emphasis added). Support for the amendment is found in the specification at, e.g., page 9, lines 21-29; page 20, lines 19-33; page 38, lines 10-26; and FIG. 1. For example, as discussed on page 9, lines 21-29, of the specification, FIG. 1 is an illustration of a gene having several exons, exons 1-4. In FIG. 1, exon 3 (103) and exon 4 (104) each has several different variants. FIG. 1 also illustrates probes that can be used for measuring the expression level of these variants. The disclosures on page 20, lines 19-33, and page 38, lines 10-26, describe the claimed method in detail.

No new matter has been added by the amendment. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-292 and 293-296 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner contends that claim 1 is vague and indefinite because the first part of the claim indicates measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes, while the second part of the claim indicates that said measuring comprises measuring the expression level of each of a plurality of different variants of said exon in one gene.

Applicants have amended claim 1 to recite that the method further comprises measuring the expression level of each of said plurality of different variants of said exon in

said at least one gene. Thus, Applicants respectfully submit that claim 1 as amended is not vague as alleged by the Examiner, and the rejection of claim 1 and dependent claims 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-292 and 293-296 under 35 U.S.C. § 112, second paragraph, is obviated and should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 1, 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285 and 289-292 are rejected under 35 U.S.C. § 102(e) as being anticipated by Penn et al., WO 01/57252 ("Penn"). Claims 7-9, 13, 160 and 286-288 are rejected under 35 U.S.C. § 102(e) as being anticipated by Penn as evidenced by Pardee et al., U.S. Patent No. 5,262,311 ("Pardee"). Claims 1, 4, 6, 11, 14-27, 31, 45, 158, 161-174, 178, 180 and 289-292 are rejected under 35 U.S.C. § 102(e) as being anticipated by Balaban et al., WO 01/081632 ("Balaban"). Applicants respectfully disagree with the Examiner for the reasons presented below[1].

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52. F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991). Anticipation requires that all aspects of the claimed invention were already described in a *single* reference. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

The presently claimed invention comprises measuring the expression level of each of a plurality of different variants of an exon of a gene, where each variant is a different splice form of the exon. Penn teaches methods and apparatuses for generating single exon probes from genomic sequence data. Penn's single exon probe is a probe comprising a sequence of an exon and, optionally, flanking intergenic or intronic sequence. Penn teaches using such single exon probes for interrogation of exon specific expression in a plurality of tissues or

[1] Applicants' response should not be construed as indicating that Applicants agree that Penn and Balaban are entitled to their priority dates and thus are properly prior art to the claimed invention. Applicants' response assumes, *solely for the sake of argument*, that Penn and Balaban are prior art.

cell types. Penn also teaches genome-derived, single exon microarrays that can be used for high throughput interrogation of exon-specific expression in a plurality of tissues or cell types.

The Examiner relies on Pardee for the teaching that mammalian cells contain approximately 15,000 different mRNA sequences.

Balaban teaches methods, compositions, and computer software for analyzing sequence variations such as products of alternative splicing. Balaban teaches using a nucleic acid probe array comprising a set of probes for interrogating the joining sequence between a first sequence element and a second sequence element. The first and second sequence elements can be a first exon and a second exon. The first and second sequence elements can also be sequence elements involved in somatic sequence recombination or RNA editing. The joining sequence is the portion of the sequence neighboring the junction between the first and second sequences. If the sequence elements are exons, the joining sequence is the 3' sequence of one exon and 5' sequence of another exon.

With respect to the rejection of claims 1, 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285 and 289-292 based on Penn, Applicants respectfully submit that Penn does not teach a gene having an exon that has a plurality of different variants, each of which is a different splice form of the exon generated using a different 3′ or 5′ splice junction of the exon. Penn does not teach a method comprising measuring the expression level of each of the plurality of different variants of such an exon. Thus, Penn does not anticipate claim 1 of the present application.

Applicants respectfully point out that although Penn uses the word "variant", the word is used to describe an mRNA variant, i.e., an mRNA molecule containing alternative exons. On the other hand, in the claims of the present application, an "exon variant" refers to a variant of an exon. Applicants respectfully direct the attention of the Examiner to the specification at page 13, lines 20-27, for a definition of a variant of an exon. As described in the specification, an exon may have several alternative 5' or 3' splice junctions. A variant of an exon is a form of the exon generated using one of such alternative splice junctions. Exon variants are also illustrated in FIG. 1 of the present application. For example, FIG.1 illustrates exons that have 3 variants (e.g., 103, i.e., exon 3; and 104, i.e., exon 4 in FIG. 1). Applicants respectfully point out that a gene can have alternatively spliced mRNA variants,

even though none of its exons has different exon variants. By way of example but not limitation, take the case of gene A having three exons, A1, A2, and A3; gene B having 3 exons, B1, B2, and B3; and gene C having 3 exons, C1, C2, and C3, wherein exon C3 has two variants C3′ and C3″. Both gene A and gene B can have different mRNA variants as a result of alternative splicing of exons A1, A2, A3 in gene A and alternative splicing of exons B1, B2, B3 in gene B, respectively, even though none of the exons in these two genes has different variants. For example, gene A can have an mRNA variant consisting of exons A1 and A2 and another mRNA variant consisting of exons A1 and A3, while none of A1, A2, A3 has different exon variants. Penn teaches determining such mRNA variants using single exon probes. In contrast, in gene C of the example, exon C3 has two variants. To determine which of the two variants of exon C3 is expressed, a single exon probe for exon C3 is not sufficient. Penn does not teach exon variants. Penn does not teach determining the expression of exon variants of any exon. Thus, Penn does not anticipate claim 1. Since Penn does not anticipate claim 1, it does not anticipate dependent claims 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285 and 289-292.

With respect to the rejection of claims 7-9, 13, 160 and 286-288 based on Penn as evidenced by Pardee, Applicants respectfully submit that the Examiner's rejection appears to be based on Penn, while using Pardee to show that Penn inherently teaches that the plurality of different genes consists of at least 100 to 10,000 different genes. Applicants respectfully point out that, as discussed above, Penn does not teach a gene having an exon that has a plurality of different variants, each of which is a different splice form of the exon generated using a different 3′ or 5′ splice junction of the exon. Penn does not teach measuring the expression level of each of the plurality of different variants of such an exon. Thus, irrespective of whether Penn inherently teaches that the plurality of different genes consist of at least 100 to 10,000 different genes, Penn does not anticipate the rejected claims.

With respect to the rejection of claims 1, 4, 6, 11, 14-27, 31, 45, 158, 161-174, 178, 180 and 289-292 based on Balaban, Applicants respectfully point out that Balaban teaches using a nucleic acid probe array comprising a set of probes for interrogating the joining sequence between a first sequence element and a second sequence element, which can be a first exon and a second exon. Balaban does not teach variants of either the first sequence element or the second sequence element. Balaban does not teach distinguishing different variants of a particular sequence element. Thus, Balaban does not explicitly teach the

claimed invention. Balaban also does not inherently disclose the claimed invention, since Balaban's teachings do not inevitably result in the practice of the claimed invention. The court held in *Continental Can Co. v. Monsanto Co.* that

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. [Citations omitted.]

Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991), quoting *In re Oelrich*, 666 F.2d 578 (CCPA 1981). Using the example discussed above, joining regions of any two different exons, either two exons none of which has variants, e.g., A1-A2, or two exons at least one of which has variants, e.g., C1-C3, can be interrogated using a set of probes as taught by Balaban. However, in cases where at least one exon has different variants, interrogating the joining region of two exons without more does not necessarily determine which of the variants of the exon is expressed. In the case of C1-C3, if C3′ and C3″ share a 5′ splice junction but have different 3′ splice junctions, interrogating the joining region of C1-C3, which contains a 3' sequence of exon C1 and a 5' sequence of exon C3′ or C3″ would not reveal whether the mRNA contains C3′ and C3″. Balaban does not teach steps for interrogating such different variants. On the other hand, if C3′ and C3″ share a 3′ splice junction but have different 5′ splice junctions, there would be two different joining regions corresponding respectively to C1-C3′ and C1-C3″. Balaban does not teach different joining regions for the two sequence elements. Balaban does not teach interrogating different joining regions of two sequence elements so as to determine the expression of the expressed variant. Therefore, Balaban does not anticipate claim 1 of the present application. Since Balaban does not anticipate claim 1, it does not anticipate dependent claims 4, 6, 11, 14-27, 31, 45, 158, 161-174, 178, 180 and 289-292.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 86, 87, 89, 90 and 265 are rejected under 35 U.S.C. § 103(a) as being obvious over Penn et al., WO 01/57252 ("Penn") in view of Friend et al., U.S. Patent No. 6,165,709 ("Friend"). Claims 293-296 are rejected under 35 U.S.C. § 103(a) as being obvious over Penn in view of DeRisi et al., 1996, Nature Genetics 14:457-460 ("DeRisi"). Applicant respectfully disagrees with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Penn has been discussed above. Friend teaches methods for identifying targets of a drug in a cell. In Friend, the effects of a drug on a cell can be determined by measuring gene expression, protein abundances, and protein activities. Friend teaches that the expression levels of a plurality of genes in a cell sample can be measured using a DNA array containing one or more binding sites for the mRNA transcribed from each gene. Thus, Friend teaches measuring the expression level of each of a plurality of genes rather than the expression levels of individual exons or multiexons in each of a plurality of genes.

DeRisi teaches determining the relative expression levels of 870 different genes in two cell samples, a tumorigenic cell line and a non-tumorigenic cell line, by measuring the hybridization levels of mRNAs corresponding to each genes using a DNA microarray containing 870 different cDNAs (see, e.g., DeRisi, page 457, left column, second full paragraph). Thus, in DeRisi, the expression level of an entire mRNA transcribed from a gene is measured by a cDNA clone on its microarray.

Applicants respectfully submit that, as discussed above, Penn does not teach or suggest a gene having an exon that has a plurality of different variants, each of which is a different splice form of the exon generated using a different 3′ or 5′ splice junction of the exon. Nor does Penn teach or suggest measuring the expression level of each of the plurality of different variants of such an exon. Thus, Penn does not render independent claim 1 obvious. Both Friend and DeRisi teach measuring the expression level of genes, not the expression levels of variants of an exon. Thus, neither Friend or DeRisi in combination with Penn renders independent claim 1 obvious, since neither Friend nor DeRisi rectify the deficiencies of Penn. Additionally, the case law is clear that "[d]ependent claims are nonobvious under section 103 if the independent claims from which they depend are

nonobvious." *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988). Thus, Applicant respectfully submits that Penn in combination with Friend does not render dependent claims 86, 87, 89, 90 and 265 obvious, and Penn in combination with DeRisi does not render claims 293-296 obvious. The rejections of these claims under 35 U.S.C. § 103(a) based on Penn in combination with Friend and on Penn in combination with DeRisi should be withdrawn.

THE NONSTATUTORY DOUBLE PATENTING REJECTIONS SHOULD BE WITHDRAWN

Claims 1, 4-27, 29-30, 36, 45, 157-175, 183 and 293-296 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,713,257 B2 ("the `257 patent"). The Examiner contends that "claims 1-39 of U.S. Patent No. 6,713,257 B2 are directed to the same subject matter and fall entirely within the scope of claims 1, 4-27, 29-30, 36, 45, 157-175, 183 and 293-296 of the present application. According to the Examiner, claims 1, 4-27, 29-30, 36, 45, 157-175, 183 and 293-296 in the instant application are anticipated by claims 1-39 of U.S. Patent No. 6,713,257 B2" (see, the instant Office Action, at page 19).

Applicants respectfully submit that the rejected claims are directed to a method for analyzing exon expression in a cell sample "*wherein said method further comprises measuring the expression level of each of said plurality of different variants of said exon in said at least one gene, each of said plurality of different variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon*; thereby analyzing the exon expression of said cell sample" (emphasis added). In contrast, claim 1 of the `257 patent is directed to a method of identifying the location of exons within the genome of a species of organism comprising: (a) contacting a sample comprising RNAs or nucleic acids derived therefrom from one or more cells of said species of organism with an array, said array comprising a positionally-addressable ordered array of polynucleotide probes bound to a solid support, said polynucleotide probes comprising a first plurality of at least 100 polynucleotide probes of different, predetermined nucleotide sequences, each said different nucleotide sequence comprising a sequence complementary and hybridizable to a different genomic sequence of the same species of organism, said respective genomic sequences for the probes being found at sequential predetermined sites in said genome of said species of organism, said contacting being under conditions conducive to hybridization between said RNAs or nucleic acids derived therefrom and said probes; (b) identifying the

one or more probes to which hybridization of one or more of said RNAs or nucleic acids derived therefrom occurs; and (c) identifying said genomic sequences for each said identified probe as the location of an exon within the genome of said species of organism. Thus, the limitation of "measuring the expression level of each of said plurality of different variants of said exon in said at least one gene, each of said plurality of different variants being a different splice form of said exon generated using a different 3′ or 5′ splice junction of said exon" of the rejected claims is not explicitly or inherently disclosed by claim 1 of the `257 patent. Claim 1 of the `257 patent does not explicitly teach measuring the expression levels of each of a plurality of variants of an exon, and claim 1 does not inherently teach such measuring because the tiled probes used in the method of claim 1 of the `257 patent does not necessarily distinguish the expression levels of individual variants of an exon (e.g., because the probes do not necessarily hybridize to the sequences that differ between the exon variants). Nor is the limitation disclosed in any one of the dependent claims 2-39. As such, claims 1-39 of the `257 patent do not anticipate claims 1, 4-27, 29-30, 36, 45, 157-175, 183 and 293-296 of the present application. Nor do the claims of the `257 patent make the rejected instant claims obvious, since there is no suggestion in the claims of the `257 patent of the measuring of the expression levels of each of a plurality of variants of an exon. The rejection under the judicially created doctrine of obviousness-type double patenting based on the `257 patent should be withdrawn.

Claims 1, 4-27, 29-30, 36, 45, 157-175, 183 and 293-296 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-114 and 177-184 of co-pending Application No. 10/813,506 ("the `506 application"). The Examiner contends that claims 1-114 and 177-184 of the `506 application are directed to the same subject matter and fall entirely within the scope of claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 of the present application. According to the Examiner, claims 1, 4-27, 29-30, 36, 45, 157-175, 183 and 293-296 in this instant application are anticipated by claims 1-114 and 177-184 of the `506 application (see, the instant Office Action, at page 20).

At the outset, Applicants respectfully submit that claims 1-114, 177 and 179-184 of the `506 application were canceled in a Preliminary Amendment filed on March 29, 2004. The rejection based on these claims is therefore obviated. Claim 178 is directed to a method for preparing an array comprising synthesizing a plurality of polynucleotide probes on a solid

support, wherein: said polynucleotide probes are ordered on said solid support so as to be positionally-addressable; said polynucleotide probes comprise a plurality of at least 100 polynucleotide probes of different nucleotide sequences; each said different nucleotide sequence comprises a sequence complementary and hybridizable to a different genomic sequence of the same species of organism; said respective genomic sequences for said polynucleotide probes are found at sequential sites in the said genome of said species of organism; the distance between 5' ends of said sequential sites is always less than 500 bp; and the genomic sequences for said plurality of probes span a genomic region of at least 25,000 bp. Thus, the limitation of "measuring the expression level of each of said plurality of different variants of said exon in said at least one gene, each of said plurality of different variants being a different splice form of said exon generated using a different 3′ or 5′ splice junction of said exon" of the rejected claims is not explicitly or inherently disclosed by claim 178 of the `506 application. Claim 178 of the `506 application does not explicitly teach measuring the expression levels of each of a plurality of variants of an exon, and claim 178 does not inherently teach such measuring because the tiled probes used in the method of claim 178 of the `506 application does not necessarily distinguish the expression levels of individual variants of an exon (e.g., because the probes do not necessarily hybridize to the sequences that differ between the exon variants). As such, claim 178 of the `506 application does not anticipate claims 1, 4-27, 29-30, 36, 45, 157-175, 183 and 293-296 of the present application. Nor does claim 178 of the `506 application make the rejected instant claims obvious, since there is no suggestion in claim 178 of the `506 application of the measuring of the expression levels of each of a plurality of variants of an exon. The provisional rejection under the judicially created doctrine of obviousness-type double patenting based on the `506 application should be withdrawn.

CLAIMS WITHDRAWN FROM CONSIDERATION AS BELONGING TO NON-ELECTED SPECIES SHOULD BE CONSIDERED

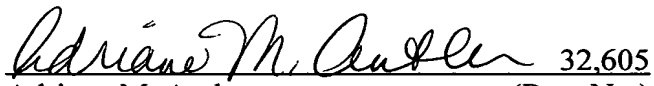
Claims 46, 88, 212, 213, 266 and 267 are withdrawn from consideration by the Examiner as belonging to non-elected species. Since Applicants believe that the generic claims are allowable, claims 46, 88, 212, 213, 266 and 267 should be considered by the Examiner. Applicants respectfully request that these claims be considered by the Examiner.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Date: February 16, 2006



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